

(www.isrec.isb-sib.ch/software/software.html). Identification of surrogates provides tools for partner identification, phenotyping and small molecule discovery. Given that a site directed assay is available at this early stage for the unknown target, high throughout screening allows the rapid identification of reactive small molecules of low target affinity. Combinatorial chemistry, allows for improvements in potency which would then provide small molecules for phenotyping and testing in animal models.

Please amend the following paragraph beginning at page 19, line 34 to page 20, line 3, to read as follows:

Sequencing of randomly selected clones from the cell library indicated that about 54% of all clones were in-frame. The short FLAG sequence DYKD(SEQ ID NO: 1), was included at the N-terminus as an immunoaffinity tag. In addition, the E-tag epitope (GAPVPYPDPLEPR) (SEQ ID NO: 2) was engineered into the carboxy terminus of the peptide.

Please amend the following paragraph beginning at page 21, line 27, to read as follows:

The panning experiments identified a surrogate peptide, KcB7, with the amino acid sequence RKEMGGGGGPGWSENLFQ(SEQ ID NO: 3). A Blastp search, using several different queries revealed TNFR1 which is the natural biological partner of TNF β .

Please amend the following section, beginning at page 21, line 34 to page 22, line 28, to read as follows:

BLASTp search results for the TNF β Surrogate peptide KcB7

Query: WSENLFQ(SEQ ID NO: 4)

Database: nr

Sequences producing significant alignments:	Score (bits)	E Value
prf 2102238A tumor necrosis factor alpha inhibitor [Homo s...	20	2419
gb AAA36756.1 (M60275) TNF receptor [Homo sapiens	20	2419
pdb 1TNR R Chain R, Tumor Necrosis Factor Receptor P55 ...	20	2419
pdb 1NCF A Chain A, Binding Protein, Cytokine Mol_id: 1; Mo...	20	2419
ref NP_001056.1 tumor necrosis factor receptor 1 (55kD) >g...	20	2419

>prf|2102238A tumor necrosis factor alpha inhibitor [Homo sapiens]
Length = 160

Score = 20.4 bits (41), Expect = 2419
Identities = 7/7 (100%), Positives = 7/7 (100%)

Query: 1 WSENLFQ 7(SEQ ID NO: 4)
WSENLFQ
Sbjct: 96 WSENLFQ 102(SEQ ID NO: 4)

>gb|AAA36756.1| (M60275) TNF receptor [Homo sapiens]
Length = 453

Score = 20.4 bits (41), Expect = 2419
Identities = 7/7 (100%), Positives = 7/7 (100%)

Query: 1 WSENLFQ 7(SEQ ID NO: 4)
WSENLFQ
Sbjct: 136 WSENLFQ 142(SEQ ID NO: 4)

>pdb|1TNR|R Chain R, Tumor Necrosis Factor Receptor P55 (Extracellular
Domain) Complexed With Tumor Necrosis Factor-Beta
Length = 139

Score = 20.4 bits (41), Expect = 2419
Identities = 7/7 (100%), Positives = 7/7 (100%)

AM

Patternfind search results for the TNF- β Surrogate peptide KcB7

Query sequence: WSENLFQ (SEQ ID NO: 4)

Please amend the following paragraph beginning at page 22, line 31 to page 23, line 8, to read as follows:

Patternfind search results for the TNF- β Surrogate peptide KcB7

Query sequence: WSENLFQ (SEQ ID NO: 4)

I. DATABASE: NONREDUNDANT

Limit 10

gp|M60275|339760|AC886035F969E231 TNF receptor [Homo sapiens]
Occurrences: 1
Position : 136 WSENLFQ (SEQ ID NO: 4)

AS

sp|P19438|TNFR1_HUMAN|4CEFBA96D03B8225 (TNFRSF1A..)TUMOR NECROSIS
FACTOR RECEPTOR 1 PRECURSOR (TUMOR NECROSIS FACTOR BINDING PROTEIN
1) (TBPI) (P60) (TNF-R1) (TNF-RI) (P55) (CD120A).[Homo sapiens]
Occurrences: 1
Position : 136 WSENLFQ (SEQ ID NO: 4)

2 matches found

Please amend the following paragraph beginning at page 23, line 10, to read as follows:

Closer examination of the complementary sequences revealed that the short N-

terminal sequence RKEMG(Piece Of SEQ ID NO: 3) and the C-terminal sequence WSENLFQ
(SEQ ID NO: 4) were identical to regions on TNFR1 (amino acids 77-81 and 107-113

AP

1A7 respectively). These segments corresponded to amino acids within two critical ligand:receptor contact domains. In the case of the N-terminal grouping, the surrogate contained 5 of the 15 amino acids of the 77-81 contact domain whereas in the C-terminal grouping, the surrogate contained 6 of the 9 amino acids identified within the 107-113 contact domain.

Please amend the following section, beginning at page 23, line 20 to page 24, line 5, to read as follows:

Comparison with human TNFR1 extracellular domain

1A7 IYPSGVIGLVPHLGDREKRDSVCPQGKYIHPQNNNSICCTKCHKGTLYNDCPGPGQDTD
CRECesgs**FT**ASENHLRhcLscSkCRkeMgQVEISSCTVDRDTCGCRKNQYRHY**WSENLE**
qcFNCSLCLNGTVHLSCQEKGQNTVCTCHAGFFLRENECVSCS (SEQ ID NO: 5)

Contact residues are based on Banner et al., (1993) Cell 73: 431-445.

Bold= contacted by TNF β subunit A

lower case = contacted by TNF β subunit C

italics = contacted by TNF β both subunits A and C

Underline = homology to the ϕ clone

TNF β

LPGVGLTPSAAQTARQHPKMHLAHSTLKPAAHLI**GDPSKQ**NSLLWR**ANTDRA**FLQDGF
SLSNN**SL**LVPTSGIYFVYSQVV**FSGK**AYSPKAPSpLyLAHEVQLFSsqypfHvPLLSSqKmV
YPGL**QEPWL**HSMYHGAA**FQLTQGDQL**SThTdGI**PHLV**LSPSTVFFGAFAL (SEQ ID NO:
6)

Bold = TNF β subunit A

lower case = TNF β subunit C

Please amend the following section, beginning at page 24, line 8, to read as follows:

Comparison with human TNFR2 extracellular domain

rKEMGGGGGpgwSENIFQ(SEQ ID NO: 7)

178 LPAQVAFTPYAPEPGSTCRLREYYDQTAQMCCSKCSPGQHAKVFCTKTSDTVCDSCEDS
TYTQLWNWVPECLSCGSRCSSDQVETQACTEQNRICTCRpgwYCAISKQEGCRLCAPLR
KCRPGFGVARPGTETSDVVCKPCAPGTFSNTTSSTDICRPHQICNVVAIPGNASRDAVCT
STSPT(SEQ ID NO: 8)

Please amend the following section beginning at page 26, line 20, to read as follows:

HCV ALIGNMENTS

eIF3: EDLDNIQTPE-SVLLSAVSGEDTQDRTDRLLLTPWVKFLWESY (SEQ ID NO: 10)

179 CONSENSUS **TxRLL** (SEQ ID NO:11)

HCV-NG-D9 TSGESSGDRTRRVLTSSSARTLPN (SEQ ID NO:12)

HCV-3-F5 LVTGQFP--SOLLLGGAVCGP-STPRLRTGLCRLSGT (SEQ ID NO:13)

HCV-3-H8 RRTC GDPAAMLERLSCRAGDYRGASHTGRLLNLRGMHQYP (SEQ ID NO: 14)

HCV-3-C3 FTTPRHLSGRTVQMMRDSTS (SEQ ID NO: 15)

Please amend the following section beginning at page 26, line 26, to read as follows:

**OUTPUT FROM ADVANCED BLAST SEARCH FOR HCV mRNA SURROGATE
QUERY - SEARCH 1:**

Query sequence: TSGESSGDRTRRVLT (SEQ ID NO: 16)
Program: blastp
Database: swissprot
Expect value: 10000

Please amend the following section, beginning at page 26, line 33 to page 28, line 35, to read as follows:

OUTPUT:

Sequences producing significant alignments:			Score E	Value
			(bits)	
sp P31258 HXAB_CHICK	HOMEBOX PROTEIN HOX-A11 (GHOX-1I) (CH...		20	477
sp P23116 IF3A_MOUSE	EUKARYOTIC TRANSLATION INITIATION FACT...		19	1072
sp P39690 KHS1_YEAST	KILLER TOXIN KHS PRECURSOR (KILLER OF ...		19	1072
sp O83264 NUSG_TREPA	TRANSCRIPTION ANTITERMINATION PROTEIN ...		19	1072
sp P13079 CARB_STRTH	RRNA METHYLTRANSFERASE		19	1072
(CARBOMYCIN-RES...				
sp Q14152 IF3A_HUMAN	EUKARYOTIC TRANSLATION INITIATION FACT...		19	1072
sp P39925 AFG3_YEAST	MITOCHONDRIAL RESPIRATORY CHAIN COMPLE...		19	1072
sp P16561 HEMA_VACCT	HEMAGGLUTININ PRECURSOR		19	1404
sp P52023 DP3B_SYNP7	DNA POLYMERASE III, BETA CHAIN		19	1404
sp P20978 HEMA_VACCC	HEMAGGLUTININ PRECURSOR		19	1404
sp P15989 CA36_CHICK	COLLAGEN ALPHA 3(VI) CHAIN PRECURSOR		19	1404

List truncated here...

>sp|P31258|HXAB_CHICK HOMEBOX PROTEIN HOX-A11 (GHOX-1I) (CHOX-1.9)

Length = 297

Score = 20.4 bits (41), Expect = 477
 Identities = 8/11 (72%), Positives = 9/11 (81%)

Query: 2 SGESSGDRTRR 12 (SEQ ID NO: 17)
 SG SSG RTR+
 Sbjct: 217 SGSSSGQRTRK 227 (SEQ ID NO: 18)

>sp|P23116|IF3A_MOUSE EUKARYOTIC TRANSLATION INITIATION FACTOR 3
 SUBUNIT 10 (EIF-3 THETA)
 (EIF3 P167) (EIF3 P180) (EIF3 P185) (P162 PROTEIN)

(CENTROSOMIN)
Length = 1344

Score = 19.2 bits (38), Expect = 1072
Identities = 8/13 (61%), Positives = 10/13 (76%)

Query: 2 SGESSGDRTRRVL 14(SEQ ID NO: 19)
SGE + DRT R+L
Sbjct: 133 SGEDTQDRTDRL 145(SEQ ID NO: 20)

>sp|P39690|KHS1_YEAST KILLER TOXIN KHS PRECURSOR (KILLER OF HEAT
SENSITIVE)
Length = 708

Score = 19.2 bits (38), Expect = 1072
Identities = 8/13 (61%), Positives = 10/13 (76%)

Query: 3 GESSGDRTRRVLT 15(SEQ ID NO: 21)
G+SSG T+R LT
Sbjct: 98 GKSSGSATKRGLT 110(SEQ ID NO: 22)

>sp|O83264|NUSG_TREPA TRANSCRIPTION ANTITERMINATION PROTEIN NUSG
Length = 185

Score = 19.2 bits (38), Expect = 1072
Identities = 7/12 (58%), Positives = 9/12 (74%)

Query: 2 SGESSGDRTRRV 13(SEQ ID NO: 23)
+GE GDRT R+
Sbjct: 117 AGEIKGDRTPRI 128(SEQ ID NO: 24)

>sp|P13079|CARB_STRTH RNA METHYLTRANSFERASE (CARBOMYCIN-
RESISTANCE PROTEIN)
Length = 299

Score = 19.2 bits (38), Expect = 1072
Identities = 8/12 (66%), Positives = 8/12 (66%)

Query: 2 SGESSGDRTRRV 13(SEQ ID NO: 23)
SG S DR RRV
Sbjct: 40 SGRSEADRRRRV 51(SEQ ID NO: 25)

>sp|Q14152|IF3A_HUMAN EUKARYOTIC TRANSLATION INITIATION FACTOR 3
SUBUNIT 10 (EIF-3 THETA)
(EIF3 P167) (EIF3 P180) (EIF3 P185) (KIAA0139)
Length = 1382

Score = 19.2 bits (38), Expect = 1072
Identities = 8/13 (61%), Positives = 10/13 (76%)

Query: 2 SGESSGDRTRRVL 14(SEQ ID NO: 19)
SGE + DRT R+L
Sbjct: 133 SGEDTQDRTRDLL 145(SEQ ID NO: 26)

>sp|P39925|AFG3_YEAST MITOCHONDRIAL RESPIRATORY CHAIN COMPLEXES
ASSEMBLY PROTEIN AFG3
(TAT-BINDING HOMOLOG 10)
Length = 761

Score = 19.2 bits (38), Expect = 1072
Identities = 8/14 (57%), Positives = 10/14 (71%)

Query: 2 SGESSGDRTRRVLT 15(SEQ ID NO: 27)
S +SGD + RVLT
Sbjct: 136 SSNNSGDDSNRVLT 149(SEQ ID NO: 28)

Please amend the following section beginning at page 29, line 1 to page 32, line 30, to read as follows:

OUTPUT FROM ADVANCED BLAST SEARCH FOR HCV mRNA
SURROGATE QUERY - SEARCH 2:

Query sequence: TSGESSGDRTRRVLTSSS(SEQ ID NO: 29)
Program: blastp
Database: swissprot
Expect value: -e 10000

Sequences producing significant alignments:	Score E (bits)	Value
sp Q01728 NAC1_RAT SODIUM/CALCIUM EXCHANGER 1 PRECURSOR (NA...	21	65
sp P70414 NAC1_MOUSE SODIUM/CALCIUM EXCHANGER 1 PRECURSOR (...)	21	65
sp P48765 NAC1_BOVIN SODIUM/CALCIUM EXCHANGER 1 PRECURSOR (...)	20	190
sp P48766 NAC1_CAVPO SODIUM/CALCIUM EXCHANGER 1 PRECURSOR (...)	20	190
sp P32418 NAC1_HUMAN SODIUM/CALCIUM EXCHANGER 1 PRECURSOR (...)	20	190
sp P23685 NAC1_CANFA SODIUM/CALCIUM EXCHANGER 1 PRECURSOR (...)	20	190
sp P48767 NAC1_FELCA SODIUM/CALCIUM EXCHANGER 1 PRECURSOR (...)	20	190

sp P08173 ACM4_HUMAN MUSCARINIC ACETYLCHOLINE RECEPTOR M4	19	249
sp P23116 IF3A_MOUSE EUKARYOTIC TRANSLATION INITIATION FACT...	19	249
sp Q14152 IF3A_HUMAN EUKARYOTIC TRANSLATION INITIATION FACT...	19	249
sp P15656 FGF5_MOUSE FIBROBLAST GROWTH FACTOR-5 PRECURSOR (...)	19	327
sp P30042 ES1_HUMAN ES1 PROTEIN HOMOLOG PRECURSOR (PROTEIN ...)	19	327
sp O35491 CLK2_MOUSE PROTEIN KINASE CLK2	18	428
sp P49760 CLK2_HUMAN PROTEIN KINASE CLK2	18	428
sp P15172 MYOD_HUMAN MYOBLAST DETERMINATION PROTEIN 1 (MYOG...	18	428
sp O75069 Y481_HUMAN HYPOTHETICAL PROTEIN KIAA0481 (HH1480)	18	428
sp P02533 K1CN_HUMAN KERATIN, TYPE I CYTOSKELETAL 14 (CYTOK...	18	561
sp P30989 NTR1_HUMAN NEUROTENSIN RECEPTOR TYPE 1 (NT-R-1) (...)	18	561
sp P30551 CCKR_RAT CHOLECYSTOKININ TYPE A RECEPTOR (CCK-A R...	18	561
sp Q08369 GAT4_MOUSE TRANSCRIPTION FACTOR GATA-4 (GATA BIND...	18	561

List truncated here...

>sp|Q01728|NAC1_RAT SODIUM/CALCIUM EXCHANGER 1 PRECURSOR
(NA+/CA2+-EXCHANGE PROTEIN 1)
Length = 971

Score = 21.2 bits (43), Expect = 65
Identities = 9/15 (60%), Positives = 11/15 (73%)

Query: 3 GESSGDRTRRVLTSS 17(SEQ ID NO: 30)
GE G RT ++LTSS
Sbjct: 933 GELGGPRTAKLLTSS 947(SEQ ID NO: 31)

>sp|P70414|NAC1_MOUSE SODIUM/CALCIUM EXCHANGER 1 PRECURSOR
(NA+/CA2+-EXCHANGE PROTEIN 1)
Length = 970

Score = 21.2 bits (43), Expect = 65
Identities = 9/15 (60%), Positives = 11/15 (73%)

Query: 3 GESSGDRTRRVLTSS 17(SEQ ID NO: 30)
GE G RT ++LTSS
Sbjct: 932 GELGGPRTAKLLTSS 946(SEQ ID NO: 32)

>sp|P48765|NAC1_BOVIN SODIUM/CALCIUM EXCHANGER 1 PRECURSOR
(NA+/CA2+-EXCHANGE PROTEIN 1)
Length = 970

Score = 19.6 bits (39), Expect = 190
Identities = 8/14 (57%), Positives = 10/14 (71%)

Query: 3 GESSGDRTRRVLTSS 16(SEQ ID NO: 33)
GE G RT ++LTS
Sbjct: 932 GELGGPRTAKLLTS 945(SEQ ID NO: 34)

>sp|P48766|NAC1_CAVPO SODIUM/CALCIUM EXCHANGER 1 PRECURSOR
(NA+/CA2+-EXCHANGE PROTEIN 1)
Length = 970

Score = 19.6 bits (39), Expect = 190
Identities = 8/14 (57%), Positives = 10/14 (71%)

Query: 3 GESSGDRTRRVLTSS 16(SEQ ID NO: 33)
GE G RT ++LTS
Sbjct: 932 GELGGPRTAKLLTS 945(SEQ ID NO: 35)

>sp|P32418|NAC1_HUMAN SODIUM/CALCIUM EXCHANGER 1 PRECURSOR
(NA+/CA2+-EXCHANGE PROTEIN 1)
Length = 970

Score = 19.6 bits (39), Expect = 190
Identities = 8/14 (57%), Positives = 10/14 (71%)

Query: 3 GESSGDRTRRVLTSS 16(SEQ ID NO: 33)
GE G RT ++LTS
Sbjct: 932 GELGGPRTAKLLTS 945(SEQ ID NO: 36)

>sp|P23685|NAC1_CANFA SODIUM/CALCIUM EXCHANGER 1 PRECURSOR
(NA+/CA2+-EXCHANGE PROTEIN 1)
Length = 970

Score = 19.6 bits (39), Expect = 190
Identities = 8/14 (57%), Positives = 10/14 (71%)

Query: 3 GESSGDRTRRVLTSS 16(SEQ ID NO: 33)
GE G RT ++LTS
Sbjct: 932 GELGGPRTAKLLTS 945(SEQ ID NO: 37)

>sp|P48767|NAC1_FELCA SODIUM/CALCIUM EXCHANGER 1 PRECURSOR
(NA+/CA2+-EXCHANGE PROTEIN 1)
Length = 970

Score = 19.6 bits (39), Expect = 190

Identities = 8/14 (57%), Positives = 10/14 (71%)

Query: 3 GESSGDRTRRVLTSS 16(SEQ ID NO: 33)
GE G RT ++LTS
Sbjct: 932 GELGGPRTAKLLTS 945(SEQ ID NO: 38)

>sp|P08173|ACM4_HUMAN MUSCARINIC ACETYLCHOLINE RECEPTOR M4
Length = 479

Score = 19.2 bits (38), Expect = 249
Identities = 8/14 (57%), Positives = 13/14 (92%)

Query: 5 SSGDRTRRVLTSSSS 18(SEQ ID NO: 39)
SSG+++ R++TSSS
Sbjct: 10 SSGNQSVRLVTSSS 23(SEQ ID NO: 40)

>sp|P23116|IF3A_MOUSE EUKARYOTIC TRANSLATION INITIATION FACTOR 3
SUBUNIT 10 (EIF-3 THETA)
(EIF3 P167) (EIF3 P180) (EIF3 P185) (P162 PROTEIN)
(CENTROSOMIN)
Length = 1344

Score = 19.2 bits (38), Expect = 249
Identities = 8/13 (61%), Positives = 10/13 (76%)

Query: 2 SGESSGDRTRRVL 14(SEQ ID NO: 19)
SGE + DRT R+L
Sbjct: 133 SGEDTQDRTDRL 145(SEQ ID NO: 20)

>sp|Q14152|IF3A_HUMAN EUKARYOTIC TRANSLATION INITIATION FACTOR 3
SUBUNIT 10 (EIF-3 THETA)
(EIF3 P167) (EIF3 P180) (EIF3 P185) (KIAA0139)
Length = 1382

Score = 19.2 bits (38), Expect = 249
Identities = 8/13 (61%), Positives = 10/13 (76%)

Query: 2 SGESSGDRTRRVL 14(SEQ ID NO: 19)
SGE + DRT R+L
Sbjct: 133 SGEDTQDRTDRL 145(SEQ ID NO: 26)

>sp|P15656|FGF5_MOUSE FIBROBLAST GROWTH FACTOR-5 PRECURSOR (FGF-5) (HBGF-5)

Length = 264

Score = 18.8 bits (37), Expect = 327
Identities = 9/16 (56%), Positives = 10/16 (62%)

Query: 3 GESSGDRTRRVLTSSS 18(SEQ ID NO: 41)
G+SSG R R T SS

Sbjct: 39 GDSSGSRGRSSATFSS 54(SEQ ID NO: 42)

>sp|P30042|ES1_HUMAN ES1 PROTEIN HOMOLOG PRECURSOR (PROTEIN KNP-I) (GT335)

Length = 268

Score = 18.8 bits (37), Expect = 327
Identities = 8/18 (44%), Positives = 11/18 (60%)

Query: 1 TSGESSGDRTRRVLTSSS 18(SEQ ID NO: 43)
T G+ S +R VLT S+

Sbjct: 93 TKGQPSEGESRNVLTESA 110(SEQ ID NO: 44)

>sp|O35491|CLK2_MOUSE PROTEIN KINASE CLK2

Length = 499

Score = 18.4 bits (36), Expect = 428
Identities = 8/11 (72%), Positives = 8/11 (72%)

Query: 2 SGESSGDRTRR 12(SEQ ID NO: 17)
S SS DRTRR

Sbjct: 34 SWSSSSDRTRR 44(SEQ ID NO: 45)

>sp|P49760|CLK2_HUMAN PROTEIN KINASE CLK2

Length = 499

Score = 18.4 bits (36), Expect = 428
Identities = 8/11 (72%), Positives = 8/11 (72%)

Query: 2 SGESSGDRTRR 12(SEQ ID NO: 17)
S SS DRTRR

Sbjct: 34 SWSSSSDRTRR 44(SEQ ID NO: 46)

Please amend the following section beginning at page 33, line 3, to read as follows:

Output from Patternfind for HCV mRNA surrogate query

Query sequence: DRTxRLL(SEQ ID NO: 47)
Database: Nonredundant
Limit: 10

sp|Q14152|IF3A_HUMAN|485C01B28D67EBBA (EIF3S10)EUKARYOTIC TRANSLATION
INITIATION FACTOR 3 SUBUNIT 10 (EIF-3 THETA) (EIF3 P167) (EIF3 P180) (EIF3 P185)
(KIAA0139).[Homo sapiens]
Occurrences: 1
Position : 139 DRTDRLL(SEQ ID NO: 48)

sp|P4637 3|FAS1_RHOFA|A66B6F3DF1286566 (FAS1..)CYTOCHROME
P450 FAS1 (EC 1.14.-.-).[Rhodococcus fascians]

Occurrences: 1
Position : 170 DRTARLL(SEQ ID NO: 49)

sp|P23116|IF3A_MOUSE|F4CAE2169F577712 (EIF3S10..)EUKARYOTIC TRANSLATION
INITIATION FACTOR 3 SUBUNIT 10 (EIF-3 THETA) (EIF3 P167) (EIF3 P180) (EIF3 P185)
(P162 PROTEIN) (CENTROSOMIN).[Mus musculus]
Occurrences: 1
Position : 139 DRTDRLL(SEQ ID NO: 50)

Please amend the following paragraph, beginning at page 34, line 15, to read as follows:

In addition, several peptides from each pan showed the presence of the **RGG** box, a well-defined RNA-binding motif, as indicated below. **RGG** sequences in each surrogate is in bold and underlined. (SEQ ID NOS 51-65, respectively, in order of appearance)

M1-3-B7	RGLFTEWFR <u>RGGS</u> WSNYRVTS
M1-3-E8	TDGGRSVISDNV <u>RGGS</u> SRLWLWIRHGWSQAWGPQDAWSSK
M1-3-H6	RVSSAQPGCTSRVRFRCPR <u>RGGLL</u> FNGVTSTNPKTGLSNAQ
M1-4-H1	VVYVGVL SYWPHLSGGGRLQVRCLIG <u>RGGF</u> GCR <u>RGG</u>
M2-3-C1	WPPGRTLSDLI <u>RGG</u> AGARGM
M2-3-C9	SSGGLHRWSAL <u>RGG</u> HGHGLA

M2-3-E2 AMRLKPIAFKGPRAGAGWVEVQPCFAAFRAACT**RGGS**SHHH
M2-3-E3 LHAGWDVTAPRRACKGAQGPGLHGRFYCH**RGGL**CSGLGRC
M2-3-E9 DEQSSLKGKLRGALVRLGMGHAMPH**RGGV**WPSTGRPSKQG
M2-3-H12 WTPRHGPMRCWRHQSVFPVGAGPHWALWPIKGPR**RGGR**TAC
M2-NG-C7 RKTGSNIWLPLYHKVCPASTRAGNG**RGGS**RFLWGSMQTNC
M3-3-B9 RLQR**RGGG**GAVAVVWVGFGVGLLWGRLLLLIILGWVLMWFLS
M3-3-C2 QHSEHGGTEWRK**RGGM**AFAASFLCMRDSYRTTRLRSLLG
M3-3-C7 GTRHVINRVRDSSGVPCKRFGGLQFSQMGKCTIP**RGGA**
M4-NG-A4 VL**RGGS**VGKGLMWCQEVDWRTGGPRSNLWGLWNGRQPPK

Please amend the following paragraph beginning at page 34, line 32 to page 35, line 4, to read as follows:

Furthermore, one sequence was found from panning the 20-mer random peptide library on target M1 that contained the KH motif, which is also a known RNA-binding motifs. The surrogate motif corresponding to the KH domain is in bold and underlined.

KH Motif **VIGxxGxxF** (SEQ ID NO: 66)
M1-3-C6 **GVIGGRGLLF**PPLSGFLHQHR (SEQ ID NO: 67)

Please amend the following paragraph beginning at page 37, line 1, to read as follows:

Sequences of Peptide Binders to Tie-1 (SEQ ID NOS 68-72, respectively, in order of appearance)

Consensus: GxAVVFLDRWGNP
>RPT13 SLWGCSGRAVLFLDSVGNPTGTVRC
>RPT9 RRVDAGGAVVYLDRWGNVSV
>RPT34 VVFLDRWGNPQYLGVKASGG
TI1-G11-R40 GPFSWLFETEWGNPKTVPFGADRWNRRHGRWDPGPVSDYGT

Please amend the following paragraph beginning at page 38, line 33 to page 39, line 2 to read as follows:

The complete ORF of the Tie-1 gene is cloned from fetal human brain (Clontech Quick-Clone cDNA) or fetal human heart using the following primers:

5' Tie-1 forward: GGT CGG CCT CTG GAG TAT GGT CTG(SEQ ID NO: 76)

3' Tie-1 reverse: TCC TTG AGG CAG CTT AAG TCA GAG(SEQ ID NO: 77)

Please amend the following paragraph beginning at page 39, line 3, to read as follows:

The complete ORF of the EGFR gene is cloned from the above libraries or from a placental cDNA library (Clontech Placenta Marathon ready cDNA) using the following primers:

5' EGFR forward: GGA GCA GCG ATG CGA CCC TC(SEQ ID NO: 78)

3' EGFR reverse: GGT CCT GGG TAT CGA AAG AGT CTG G(SEQ ID NO: 79)

Please amend the following paragraph, beginning at page 39, line 10, to read as follows:

In the chimeric receptor, the extracellular and transmembrane regions of Tie-1 are joined to the cytoplasmic kinase domain of the EGFR with an NHE I site which will add the amino acids alanine and serine at the junction. The primers for generating the chimeric receptor are the following primers (with the NHE site underlined):

EGFR forward: GCG CTG CTA GCC GAA GGC GCC ACA TCG TTC(SEQ ID NO: 80)

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Tie-1 reverse: GCT GCT GCT AGC GAT GCA CAC CAG GGT TAA AAG G

(SEQ ID NO: 81)

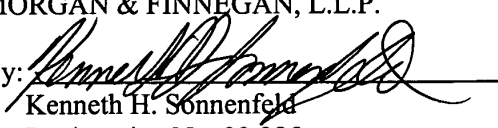
Should any fees be required by the filing of this Response, Amendment, Statement, and Sequence Listing, authorization is hereby given to charge the amount of any such fee(s) that is/are properly assessable in this application to Deposit Account No. 13-4500, Docket No. 2598-4004US1. **A DUPLICATE COPY OF THIS SHEET IS ATTACHED.**

Respectfully submitted,

MORGAN & FINNEGAN, L.L.P.

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